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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/004,381	10/31/2001	Jack W. Szostak	00786/388002	7263

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SNEDDEN, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/004,381	SZOSTAK ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *15,16 and 20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17-19* is/are rejected.

7)☒ Claim(s) *10-14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/30/04, 3/24/03,*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of invention I, claims 1-14 and 17-19 and SEQ ID NO: 25 in paper filed 20 January 2004 is acknowledged. Claims 15-16, 20-27 and SEQ ID NO: 1-24 and 26-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. Election was made **with** traverse. Applicant argues that there would be no serious burden on the Office to search a reasonable number of Applicants' claimed peptides. Applicants request that the restriction requirement be withdrawn and Applicants be given the opportunity to elect at least 10 different, individual peptides for examination.

Applicant's argument is consider but is not found persuasive for the following reasons. As stated in the office action mailed, the different proteins represent different inventions and require different, non-contiguous searches. In addition, the claims do not recite a common structure representative of a genus or class of peptides, only individual peptides with a distinct structures are claimed. Thus to consider all, or 10, peptides would constitute an undue burden because each requires considerations that are separate from each of the others. The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

3. Claims 10-14 is objected to because of the following informalities: As SEQ ID NO: 25 has been elected, claims 10-14 recites nonelected subject matter withdrawn from consideration. Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. Claims 1-14 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. As stated, the claims recite a peptide of natural origin and do not show the hand of man. Applicant is advised to include the words "isolated" or "purified" in the recitation of the invention directed towards protein to indicate the hand of man.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Claims 1-9 and 17-19 recite a genus of peptide ligands, and fusion protein thereof, that possess the function of high affinity binding to streptavidin. Claim 1, and dependent claims 4-7, are limited the peptide structure to non-cyclic and non-disulfide bonded peptides. Claim 2, and dependent claims 4-7, recite the exclusion of the HPQ motif in the structure of the peptide. Claim 3, and dependent claims 8-9, do not limit the structure of the peptide ligands. Claim 17, and dependent claims 18-19, incorporate the language of all three of the above independent claims.

A review of the full content of the specification and the prior art indicates that the presence of the HPQ motif in a peptide is suggestive of a binding domain for streptavidin. However, the specification indicates that the presence of two HPQ motifs was not sufficient for high affinity binding and that zero HPQ motifs in the linear structure is not required for binding (page 27 and Table 1). The prior art describes cyclic peptides having the HPQ domain with a Kd of less than 10 μM, however, linear peptides with a Kd of less than 10 μM are unknown (Giebel *et al.;* regarding claim 1). Furthermore, the prior art teaches many linear and cyclic peptides containing the HPQ motif, however, none have the Kd of less than 23 nM (Giebel *et al.;* regarding claim 3). Thus, the presence of the HPQ domain is insufficient to link structure with the function of a Kd of less than 10 μM or 23 nM. No other unifying structural characteristic is described in the specification. The instant specification fails to provide sufficient descriptive information for the structural and functional relationship of the claimed genus of polypeptides comprising the HPQ domain.

The above analysis only considered the presence of the HPQ domain. However, the instant specification also fails to provide sufficient descriptive information for the structural and

functional relationship of the claimed genus of polypeptides not comprising the HPQ domain. Outside the description of the HPQ domain, there is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the amino acids in which variability may be tolerated and there is no information regarding the relation of structure to function. Additional, structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the peptides encompassed. No identifying characteristic or property of the instant peptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. For example, Table 1 provides for a single peptide ligand in which does not possess the HPQ domain, indicating that the HPQ domain is not required. However, one peptide is not representative of the entire genus of peptide not comprising the HPQ domain as is presently claimed.

The claims, as written, encompass peptides that vary substantially in length and also in amino acid composition, which may or may not comprise the HPQ domain. Thus, the structure of the peptide ligand would seem to be highly variant. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific peptide and the ability to screen is insufficient to describe the genus as claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Therefore, only linear peptides comprising the HPQ domain possessing the function of high affinity binding to streptavidin, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4-7 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a high-affinity, streptavidin, peptide ligand comprising an HPQ domain, does not reasonably provide enablement for all peptides ligands absent the HPQ domain. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the breadth of the claims,
3. the state of the prior art,
4. the predictability or lack thereof in the art,
5. the amount of direction or guidance present,
6. the presence or absence of working examples,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) the nature of the invention;

The invention is a set of identified peptide ligands that bind to streptavidin with high affinity. The unifying characteristics of these peptides are that they are non-cyclical and do not have disulfide bonds. Additionally, the claims 2, 4-7 and 17-19 recite to absence of an HPQ or similar domain.

2) the breadth of the claims;

In the instant case, Applicants are claiming all proteins, which are non-cyclic and do not possess a disulfide bond, that will bind to streptavidin with at least a Kd of 10 μM. Claims 2, 4-7, and 17-19 further include the exclusion of peptides that possess a HPQ domain, and thus read upon any protein not containing the HPQ motif. Fusion proteins of any protein not containing the HPQ motif are also claimed.

3) the state of the prior art;

4) the predictability or unpredictability of the art;

Cyclic and dimerized peptides are described in the art as high affinity ligands for streptavidin (Katz, Biochemistry 1995). Additionally, the prior art teaches linear peptide ligands for streptavidin. These peptides share the presence of an HPQ motif and a person of skill in the art could reasonably predict that a peptide containing one or more HPQ motifs may bind streptavidin. However, without the presence of this motif, it cannot be predicted that the peptide will bind to streptavidin.

5) the amount of direction or guidance presented;
6) the presence or absence of working examples;

The specification describes the methods to isolated linear peptides capable of binding streptavidin with high affinity. The specification walks us through the steps from the generation of a streptavidin-binding peptide library to the identification of peptides binding streptavidin (pages 21-25, for example). Most of the peptides described in the specification contain at least one HPQ motif, however, one peptide, identified as SB20, does not contain such a domain (see table 1, page 16-17). At page 27, the specification indicates that the presence of two HPQ motifs was not sufficient for high affinity binding. However, no guidance is provided as to what is sufficient absent a HPQ motif.

Other than the number of HPQ domains, the specification does not identify any other unifying property that is maintained among the peptides. However, HPQ is not claimed, and in fact, is excluded from the scope of the invention in claims 2, 4-7 and 17-19. A unifying characteristic for the claim peptides, necessary to define a genus, is not defined by the claims and is not taught by the specification. A person of skill in the art would not be able to make or used a peptide commensurate with the scope of the claims. Only the peptide that is specifically taught by the specification, SB20 (Table 1), is enabled.

7) the quantity of experimentation necessary;

Given the status of the art and guidance in the specification, a person of skill in the art could not produce a functional molecule for every instance within the scope of the claim. The courts have interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). As such, the quality of experimentation necessary to identify and qualify every peptide absent an HPQ domain for binding to streptavidin is undue.

8) the relative skill of those skilled in the art;

In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a PhD or a person with several years of experience in the art. As the cited art would point to, even with a level of skill in the art that is high, predictability of the results is not invariable.

In consideration of each of factors 1 – 8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-14 recite the peptide of SEQ ID NO: 25 that contains an HPQ domain. However, the claims depend from claim 2 which excludes the presence of an HPQ domain. This contradiction renders the claims indefinite.

Claims 12 and 13 recite the peptide of SEQ ID NO: 25 that contains 38 amino acids. Claims 12 and 13 limit SEQ ID NO: 25 to 50 and 100 consecutive amino acids, respectively. There is insufficient antecedent basis for these limitations and thus, the claims are rendered indefinite.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9 and 17-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Nolan *et al.* . Nolan *et al.* teaches a GFP fusion protein that is absent any disulfide bonds, absent an HPQ or similar domain, and is not cyclized. The fusion protein of Nolan *et al.* comprises GFP fused to a peptide segment that is biotinylated by the biotin holoenzyme synthetase (biotin ligase) in E. coli (see column 3). This biotinylated enhanced GFP binds to avidin, or streptavidin, with a Kd of 4nM (column 3, line 10). Thus, the reference anticipates the claimed invention.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (571) 272-0959. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for

regular communications to the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
February 23, 2004
SKS

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER